

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
WO 2006/100154 A1

(51) International Patent Classification:
A61L 15/44 (2006.01) A61L 27/54 (2006.01)
A61L 27/34 (2006.01)

(74) Agent: KRAHBICHLER, Erik; Ström & Gulliksson AB,
Järnvägsatan 3, S-252 24 Helsingborg (SE).

(21) International Application Number:
PCT/EP2006/050884

(22) International Filing Date:
13 February 2006 (13.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
05006474.0 24 March 2005 (24.03.2005) EP
60/666,504 30 March 2005 (30.03.2005) US
05018269.0 23 August 2005 (23.08.2005) EP
60/711,006 24 August 2005 (24.08.2005) US

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): NOLABS
AB [SE/SE]; Kungsgatan 6, S-252 21 Helsingborg (SE).

Published:

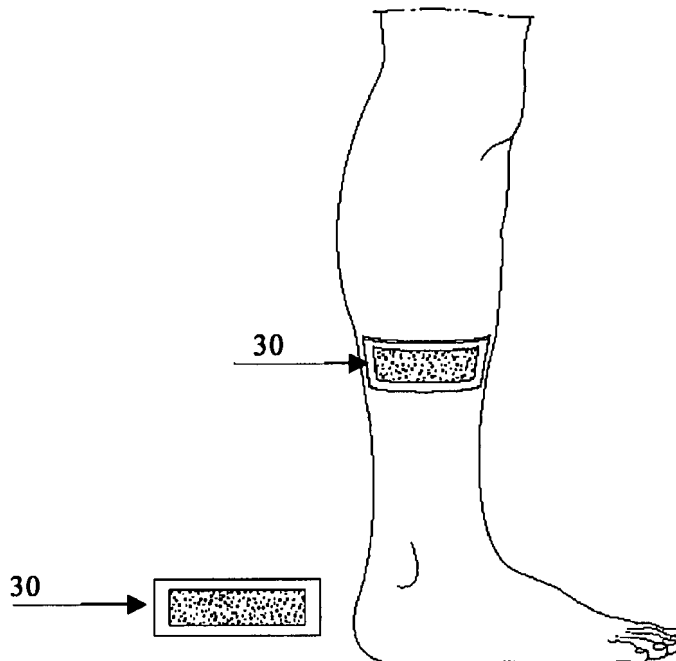
— with international search report

(72) Inventor; and

(75) Inventor/Applicant (for US only): PETERS, Tor
[SE/CH]; Chalet Marabou Bodemos, CH-1659 Rouge-
mont (CH).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COSMETIC TREATMENT WITH NITRIC OXIDE, DEVICE FOR PERFORMING SAID TREATMENT AND MANUFACTURING METHOD THEREFOR



(57) Abstract: A cosmetic treatment method, and a device therefor, are provided that allow for cosmetic treatment of cosmetic disorders, caused by chronological age, environmental factors, changes in physiological functions of skin, such as psoriasis, dermatitis, acne, cellulites, and viral and/or bacteriological attacks. The device comprises a nitric oxide (NO) eluting polymer arranged to contact the area to be cosmetically treated, such that a cosmetic dose of nitric oxide is eluted from said nitric oxide eluting polymer to said area. The nitric oxide (NO) eluting polymer is integrated with a carrier material, such that said carrier material, in use, regulates and controls the elution of said cosmetic dosage of nitric oxide (NO). Furthermore, a manufacturing method for said device is provided.

**COSMETIC TREATMENT WITH NITRIC OXIDE, DEVICE FOR PERFORMING
SAID TREATMENT AND MANUFACTURING METHOD THEREFOR**

Field of the Invention

5 This invention pertains in general to the field of
cosmetic treatment, involving the use of nitric oxide (NO).
More particularly the invention relates to a device for
performing said treatment, and a process for manufacturing
of said device, involving the use of nitric oxide (NO) for
10 cosmetic purposes.

Background of the Invention

 In the society of today there is an increasing demand
for products that will improve the physiological visual
15 appearance of human beings.

 Chronological age, environmental factors, changes in
physiological functions of skin, psoriasis, dermatitis,
cellulites, viral and/or bacteriological attacks, are some
factors that affect the appearance of human beings in a
20 cosmetically undesirable way.

 Many of the alterations mentioned above are caused by
changes in the outer epidermal layer of the skin, while
others are caused by changes in the lower part of dermis.
For instance, chronological age and extensive exposure to
25 environmental factors, such as sun radiation, affect dermis
in such way that dermis undergoes structural and functional
changes, which result in many of the characteristics of
aged skin, such as loss of elasticity, formation of
wrinkles, loss of water-holding capacity, uneven
30 distribution of fat, cellulites and sagging.

 One thing that these factors have in common is that
they are obtained by the loss of blood perfusion in the
affected tissues.

 Viral and bacteriological attacks may also result in
35 impaired cosmetic appearance. Examples of such viral or
bacteriological attack are herpes, such as Herpes Simplex
Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2),

Epstein Barr Virus (EBV), CytoMegalovirus (CMV), Varicella Zoster Virus (VZV), human herpes virus 6 (*exanthum subitum* and *roseola infantum*), human herpes virus 8 (HHV-8), caposis sarcoma, probably caused by HHV-8, genital warts or
5 warts, such as *verruca vulgaris*, *verruca planae*, *verruca seborroica*, filiform warts, mosaic warts, etc., caused by virus, and molluscs, caused by poxvirus. Such attacks lead often to cosmetically unaccepted skin defects, such as scars.

10 Psoriasis, such as *invers psoriasis*, *psoriasis guttata*, *psoriasis pustulosa* etc., is an inflammatory reaction in the skin, that may appear as a consequence of infection of *Streptococcus*. The disorder is not a self-healing disorder, and has to be treated, if the person
15 suffering from psoriasis finds the disorder disfiguring or affecting his/her appearance in an undesirable way. Treatment of psoriasis is restricted to anti-inflammatory substances, such as glucocorticosteroids. This kind of treatment is often accompanied by adverse side effects,
20 such as skin atrophy, telangiectasia, striae, hypertrichosis, rosacea, and dermatitis.

Dermatitis is another skin disorder that may disfigure a person, or affect the visual appearance of the person in a negative way.

25 The techniques according to the prior art, in respect of chronological age, environmental factors, changes in physiological functions of skin, include numerous of physiological, chemical, and mechanical methods, such as treatment with hydroxy acids, retinoids, barrier
30 disrupters, tape stripping, solvent extraction etc. These methods present various drawbacks, such as irritation of the skin, skin toxicity, the requirement of high concentrations of expensive ingredients, pH values that are incompatible with the optimum pH value of the skin, long
35 and cumbersome trials to establish whether or not a

specific compound or composition is toxic or not, etc.
Furthermore, the majority of the cosmetic methods according
to the prior art induce invocation of damage of the skin,
which results in the in set of repair mechanisms. Hence,
5 there will be a period of time, such as weeks or months,
during which the skin will remain irritated, and after
which tolerance sets in and the irritations will diminish.

Up to this point there is no method, composition,
compound etc., with the ability to simultaneously treat and
10 prevent cosmetically undesirable disorders originating from
both physiological factors, such as chronological age,
environmental factors, changes in physiological functions
of skin, such as psoriasis, dermatitis, cellulites, etc.,
and viral and bacteriological attacks.

15 Nitric oxide (NO) is a highly reactive molecule that
is involved in many cell functions. In fact, nitric oxide
plays a crucial role in the immune system and is utilized
as an effector molecule by macrophages to protect itself
against a number of pathogens, such as fungi, viruses,
20 bacteria etc., and general microbial invasion. This
improvement of healing is partly caused by NO inhibiting
the activation or aggregation of blood platelets, and also
by NO causing a reduction of inflammatory processes at the
site of an implant.

25 NO is also known to have an anti-pathogenic,
especially an anti-viral, effect, and furthermore NO has an
anti-cancerous effect, as it is cytotoxic and cytostatic in
suitable concentrations, i.e. it has among other effects
tumoricidal and bacteriocidal effects. NO has for instance
30 cytotoxic effects on human haematological malignant cells
from patients with leukaemia or lymphoma, whereby NO may be
used as a chemotherapeutic agent for treating such
haematological disorders, even when the cells have become
resistant to conventional anti-cancer drugs. This anti-
35 pathogenic and anti-tumour effect of NO is taken advantage

of by the present invention for cosmetic purposes, without having adverse effects.

However, due to the short half-life of NO, it has hitherto been very hard to treat viral, bacteria, virus, fungi or yeast infections with NO. This is because NO is actually toxic in high concentrations and has negative effects when applied in too large amounts to the body.

NO is actually also a vasodilator, and too large amounts of NO cause for instance a complete collapse of the circulatory system. On the other hand, NO has a very short half-life of fractions of a second up to a few seconds, once it is released. Hence, administration limitations due to short half-life and toxicity of NO have been limiting factors in the use of NO in the field of anti-pathogenic and anti-cancerous treatment so far.

In recent years research has been directed to polymers with the capability of releasing nitrogen oxide when getting in contact with water. Such polymers are for example polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) and B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible with natural products, after the release of nitrogen oxide.

Other example for NO eluting polymers are given in US-5,770,645, wherein polymers derivatized with at least one $-NO_x$ group per 1200 atomic mass unit of the polymer are disclosed, X being one or two. One example is an S-nitrosylated polymer and is prepared by reacting a polythiolated polymer with a nitrosylating agent under conditions suitable for nitrosylating free thiol groups.

Akron University has developed NO-eluting L-PEI molecule that can be nano-spun onto the surface of medical devices to be permanently implanted in the body, such as implanted grafts, showing significant improvement of the healing process and reduced inflammation when implanting such devices. According to US-6,737,447, a coating for

medical devices provides nitric oxide delivery using nanofibers of linear poly(ethylenimine)-diazoniumdiolate. Linear poly(ethylenimine)diazoniumdiolate releases nitric oxide (NO) in a controlled manner to tissues and organs to aid the healing process and to prevent injury to tissues at risk of injury.

However, the meaning of "controlled" in the context of US 6,737,447 is only directed to the fact that nitric oxide is eluted from the coating during a period of time. Therefore, the interpretation of "controlled" in respect of US 6,737,447 is different from the meaning of "regulating" in the present invention. "Regulate", according to the present invention is intended to be interpreted as the possibility to vary the elution of nitric oxide to thereby achieve different elution profiles.

Electrospun nano-fibers of linear poly(ethylenimine) diazoniumdiolate deliver therapeutic levels of NO for cosmetic purposes to the tissues surrounding a medical device while minimizing the alteration of the properties of the device. A nanofiber coating, because of the small size and large surface area per unit mass of the nanofibers, provides a much larger surface area per unit mass while minimizing changes in other properties of the device.

However, the disclosure is both silent concerning an improvement of present technology in respect of cosmetic treatment of physiologically factors, disorders, such as psoriasis and dermatitis, and viral and/or bacteriological attacks, by the use of NO.

Hence, an improved, and more advantageous, method and device for the treatment and/or prevention of cosmetic disorders is desired. These cosmetic disorders comprise cosmetic disorders, which are caused by chronological age, environmental factors, changes in physiological functions of skin, psoriasis, dermatitis, cellulites, viral and/or bacteriological attacks. It is desired that the method and

device do not develop resistance against the active pharmaceutical substance, and which preferably during the cosmetical treatment does not cause or causes minimal local skin irritation or contact allergic reactions, skin toxicity, the requirement of high concentrations of expensive ingredients, pH values that are incompatible with the optimum pH value of the skin, long and cumbersome trials to establish whether or not a specific compound or composition is toxic or not, skin atrophy, telangiectasia, striae, hypertrichosis, rosacea, dermatitis etc, would be advantageous, and in particular a method and device allowing for target improvement of the visual appearance would be advantageous.

Summary of the Invention

Accordingly, the present invention preferably seeks to mitigate, alleviate or eliminate one or more of the above-identified deficiencies in the art and disadvantages singly or in any combination and solves, among others, the problems mentioned above, by providing an advantageous cosmetic treatment, a device for said cosmetic treatment, a manufacturing method for the latter and a use of nitric oxide according to the appended patent claims.

According to one aspect of the invention, a cosmetic treatment is provided that allows for target treatment of cosmetic disorders, caused by chronological age, environmental factors, changes in physiological functions of skin, such as psoriasis, dermatitis, cellulites, and viral and/or bacteriological attacks, for example herpes, such as Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Epstein Barr Virus (EBV), CytoMegalovirus (CMV), Varicella Zoster Virus (VZV), human herpes virus 6 (*exanthum subitum* and *roseola infantum*), human herpes virus 8 (HHV-8), caposis sarcoma, probably caused by HHV-8, warts, such as *verruca vulgaris*, *verruca*

planae, *verruca seborroica*, filiform warts, mosaic warts, etc., caused by virus, and molluscs, caused by poxvirus. The cosmetic method comprises an application of a nitric oxide (NO) eluting polymer arranged to contact the area to be treated, such that a cosmetic dose of nitric oxide is eluted from said nitric oxide eluting polymer to said area.

According to another aspect of the invention, a device is provided that allows for target treatment of cosmetic disorders, caused by chronological age, environmental factors, changes in physiological functions of skin, such as psoriasis, dermatitis, cellulites, and viral and/or bacteriological attacks, for example herpes, such as Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Epstein Barr Virus (EBV), CytoMegaloVirus (CMV), Varicella Zoster Virus (VZV), human herpes virus 6 (*exanthum subitum* and *roseola infantum*), human herpes virus 8 (HHV-8), caposis sarcoma, probably caused by HHV-8, warts, such as *verruca vulgaris*, *verruca plana*, *verruca seborroica*, filiform warts, mosaic warts, etc., caused by virus, and molluscs, caused by poxvirus. The device comprises a nitric oxide (NO) eluting polymer arranged to contact the area to be treated, such that a cosmetic dose of nitric oxide is eluted from said nitric oxide eluting polymer to said area.

According to another aspect of the invention, a manufacturing process for such a cosmetic treatment device is provided, wherein the process is a process for forming a device that allows for target treatment of cosmetic disorders, caused by chronological age, environmental factors, changes in physiological functions of skin, such as psoriasis, dermatitis, cellulites, and viral and/or bacteriological attacks, for example herpes, such as Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Epstein Barr Virus (EBV), CytoMegaloVirus (CMV), Varicella Zoster Virus (VZV), human herpes virus 6

(*exanthum subitum* and *roseola infantum*), human herpes virus 8 (HHV-8), caposis sarcoma, probably caused by HHV-8, warts, such as *verruca vulgaris*, *verruca planae*, *verruca seborroica*, filiform warts, mosaic warts, etc., caused by virus, and molluscs, caused by poxvirus. The process comprises selecting a plurality of nitric oxide eluting polymeric particles, such as nano fibres, fibres, nano particles, or microspheres, and deploying said nitric oxide eluting particles in a condom/sheath or tape/coating to be comprised in said device. Alternatively the NO eluting particles are admixed to an ointment, cream, gel or foam.

The present invention has at least the advantage over the prior art that it provides target exposure of an area to be cosmetically treated to NO, whereby blood perfusion and vasodilatation are increased, whereby the supply of nutrients increase, simultaneously as an anti-viral, and an anti-microbial, effect is achievable.

Brief Description of the Drawings

These and other aspects, features and advantages of which the invention is capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which

Figs. 1A and 1B are schematic illustrations of a condom/sheath according to an embodiment of the device of the present invention,

Figs. 2A and 2B, are schematic illustrations of a tape or coating according to an embodiment of the device of the present invention,

Fig. 2C is a schematic illustration of a sock according to an embodiment of the device of the present invention,

Fig. 3 is a schematic illustration of a patch/pad according to an embodiment of the device of the present invention, and

Fig. 4 is chart showing an illustration of two different elution profiles for two different mixtures of nitric oxide eluting polymer and carrier material.

Description of Embodiments

The following description focuses on embodiments of the present invention applicable to a device, which allows for target treatment of cosmetic disorders, for instance caused by chronological age, environmental factors, changes in physiological functions of skin, acne, psoriasis, dermatitis, cellulites, viral and/or bacteriological attacks, such as herpes, for example Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Epstein Barr Virus (EBV), CytoMegalovirus (CMV), Varicella Zoster Virus (VZV), human herpes virus 6 (*exanthum subitum* and *roseola infantum*), human herpes virus 8 (HHV-8), caposis sarcoma, probably caused by HHV-8, warts, such as *verruca vulgaris*, *verruca planae*, *verruca seborroica*, filiform warts, mosaic warts, etc., caused by virus, and molluscs, caused by poxvirus.

With regard to nitric oxide (nitrogen monoxide, NO), its physiological and pharmacological roles have attracted much attention and thus have been studied. NO is synthesized from arginine as the substrate by nitric oxide synthase (NOS). NOS is classified into a constitutive enzyme, cNOS, which is present even in the normal state of a living body and an inducible enzyme, iNOS, which is produced in a large amount in response to a certain stimulus. It is known that, as compared with the concentration of NO produced by cNOS, the concentration of

NO produced by iNOS is 2 to 3 orders higher, and that iNOS produces an extremely large amount of NO.

In the case of the generation of a large amount of NO as in the case of the production by iNOS, it is known that
5 NO reacts with active oxygen to attack exogenous microorganisms and cancer cells, but also to cause inflammation and tissue injury. On the other hand, in the case of the generation of a small amount of NO as in the case of the production by cNOS, it is considered that NO
10 takes charge of various protective actions for a living body through cyclic GMP (cGMP), such as vasodilator action, improvement of the blood circulation, antiplatelet-aggregating action, antibacterial action, anticancer action, acceleration of the absorption at the digestive
15 tract, renal function regulation, neurotransmitting action, erection (reproduction), learning, appetite, and the like. Heretofore, inhibitors of the enzymatic activity of NOS have been examined for the purpose of preventing inflammation and tissue injury, which are considered to be
20 attributable to NO generated in a large amount in a living body. However, the promotion of the enzymatic activity (or expressed amount) of NOS (in particular, cNOS) has not been examined for the purpose of exhibiting various protective actions for a living body by promoting the enzymatic
25 activity of NOS and producing NO appropriately.

In recent years research has been directed to polymers with the capability of releasing nitrogen oxide when getting in contact with water. Such polymers are for example polyalkyleneimines, such as L-PEI (Linear
30 PolyEthyleneImine) and B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible. Another advantage is that NO is released without any secondary products that could lead to undesired side effects. NO is released without by-products or breakdown
35 products.

The polymers according to the present invention may be manufactured by electro spinning, air spinning, gas spinning, wet spinning, dry spinning, melt spinning, or gel spinning. Electro spinning is a process by which a
5 suspended polymer is charged. At a characteristic voltage a fine jet of polymer releases from the surface in response to the tensile forces generated by interaction by an applied electric field with the electrical charge carried by the jet. This process produces a bundle of polymer
10 fibres, such as nano-fibres. This jet of polymer fibres may be directed to a surface to be treated.

Furthermore, US 6,382,526, US 6,520,425, and US 6,695,992 disclose processes and apparatuses for the production of such polymeric fibres. These techniques are
15 generally based on gas stream spinning, also known within the fiber forming industry as air spinning, of liquids and/or solutions capable of forming fibers.

Other example for NO eluting polymers are given in US-5,770,645, wherein polymers derivatized with at least
20 one -NOX group per 1200 atomic mass unit of the polymer are disclosed, X being one or two. One example is an S-nitrosylated polymer and is prepared by reacting a polythiolated polymer with a nitrosylating agent under conditions suitable for nitrosylating free thiol groups.

25 Akron University has developed NO-eluting L-PEI molecule that can be nano-spun onto the surface of permanently implanted medical devices, such as implanted grafts, showing significant improvement of the healing process and reduced inflammation when implanting such
30 devices. According to US-6,737,447, a coating for medical devices provides nitric oxide delivery using nanofibers of linear poly(ethylenimine)-diazoniumdiolate. Linear poly(ethylenimine)diazoniumdiolate releases nitric oxide (NO) in a controlled manner.

However, the meaning of "controlled" in the context of US 6,737,447 is only directed to the fact that nitric oxide is eluted from the coating during a period of time, i.e. that the nitric oxide is not eluted all in once.

5 Therefore, the interpretation of "controlled" in respect of US 6,737,447 is different from the meaning of "regulating" in the present invention. "Regulate or control", according to the present invention is intended to be interpreted as the possibility to vary the elution of nitric oxide to
10 thereby achieve different elution profiles.

A polymer comprising an O-nitrosylated group is also a possible nitric oxide eluting polymer. Thus, in one embodiment of the present invention, the nitric oxide eluting polymer comprises diazeniumdiolate groups, S-
15 nitrosylated and O-nitrosylated groups, or any combinations thereof.

In still another embodiment of the present invention said nitric oxide eluting polymer is a poly(alkyleneimine)diazeniumdiolate, such as L-PEI-NO
20 (linear poly(ethyleneimine)diazeniumdiolate), where said nitric oxide eluting polymer is loaded with nitric oxide through the diazeniumdiolate groups and arranged to release nitric oxide at a treatment site.

Some other examples of a suitable nitric oxide
25 eluting polymer are selected from the group comprising mino cellulose, amino dextrans, chitosan, aminated chitosan, polyethyleneimine, PEI-cellulose, polypropyleneimine, polybutyleneimine, polyurethane, poly(buthanediol spermate), poly(iminocarbonate), polypeptide, Carboxy
30 Methyl Cellulose (CMC), polystyrene, poly(vinyl chloride), and polydimethylsiloxane, or any combinations of these, and these mentioned polymers grafted to an inert backbone, such as a polysaccharide backbone or cellulosic backbone.

In still another embodiment of the present invention
35 the nitric oxide eluting polymer may be an O-derivatized

NONOate. This kind of polymer often needs an enzymatic reaction to release nitric oxide.

Other ways of describing polymers, which may be suitable as nitric oxide eluting polymer, is polymers
5 comprising secondary amine groups ($=N-H$), such as L-PEI, or have a secondary amine ($=N-H$) as a pendant, such as aminocellulose.

In one embodiment the device is in form of fibres, nano-particles, or micro-spheres of a NO eluting polymer,
10 which fibres, nano-particles, or micro-spheres are be integrated in a gel, cream, or foam, that may either be in a smearing or compressed structure.

In still another embodiment the nitric oxide eluting polymer, such as powder, nano-particles or micro-spheres,
15 may be incorporated in foam. The foam may have an open cell structure, which facilitates the transport of the proton donor to the nitric oxide eluting polymer. The foam may be of any suitable polymer such as polyethylene, polypropylene, polyacrylonitrile, polyurethane,
20 polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable
25 polymers, cotton polyolefins, and latex, or any combinations of these.

In another embodiment the device is in form of a cream, a gel or a combination of the two. Since the nitric oxide eluting polymer is activated by proton donors the
30 nitric oxide eluting polymer has to be separate from the proton donor until one wants to initiate the elution of nitric oxide, i.e. use the device. One way to accomplish this is to have a syringe with two separate containers. One of the containers contains a proton donor-based gel and in
35 the other container a non proton donor-based gel,

comprising the nitric oxide eluting polymer, is contained. Upon using the syringe like device, the two gels are squeezed from the syringe and mixed together, whereupon the proton donor in the first gel comes in contact with the
5 nitric oxide eluting polymer in the second gel and the elution of nitric oxide starts. That means, two components are advantageously admixed from a self-contained unit upon administration to a cosmetic treatment site.

These fibres, nano-particles, or micro-spheres, may
10 be formed from the NO-eluting polymers comprised in the present invention, for example polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) and B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible, after the release of nitrogen oxide.
15 They may also be encapsulated in any suitable carrier material, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol,
20 polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

In the context of the present invention the term
25 "encapsulating" is intended to be interpreted as fixating the nitric oxide eluting polymer in a three dimensional matrix such as a foam, a film, a nonwoven mat of nano-fibers or fibers, other materials with the capability to fixate the NO eluting polymer, or enclosing the nitric
30 oxide eluting polymer in any suitable material.

According to an embodiment, the device is in the form of a lipstick-like device, which makes the NO especially easily applied to the skin or lips. Alternatively the gel cream, or foam is in form of or a dermatological ointment,

cream or lotion for easy application to the body, e.g. in form of a spray bottle or a tube for easy application.

The device according to the present invention is applied on the area to be treated, such as any part of the body in need of improved cosmetic appearance, such as the face, neck, shoulders, hands, arms, back, chest, stomach, bottom, thigh, genitals, lower leg, and/or foot. Some places on the human body are of special interest for a majority of the population, such as the face, for the treatment of cosmetic deficiencies caused by or related to herpes, acne, wrinkles, sagging, loss of elasticity, loss of water-holding capacity, uneven distribution of fat, and the thigh, for the treatment of cellulites. Although these body parts commonly attract the most interest of the population, the present invention is not in any way intended to be limited to these.

When the gel, cream, or foam according to the present invention has been applied an elution of NO is initiated by adding a proton donor, such as water, in any possible way. This may for example be accomplished by applying a water soaked patch on said gel, gel, cream, or foam, or spraying or bathing said gel, cream, or foam with water.

The cosmetic effect is obtained, as the NO eluting polymer elutes NO on the area to be treated, by an increased blood perfusion and vasodilatation, whereby an increased supply of nutrients in the tissue of interest is achieved. The increased blood perfusion and vasodilatation may, in another embodiment of the present invention, result in an improved effect when combined with other skin care products. Thus, this synergistic effect is within the scope of the present invention.

The fibres, nano-particles, or micro-spheres may also be integrated in a hydrogel, which is mixed directly before use.

This embodiment has the advantage of being able to penetrate pockets and corners in the skin for closer elution of NO on the area to be treated.

In another embodiment, according to Figs. 1A and 1B,
5 the device according to the present invention is in form of a latex or rubber condom/sheath, said condom/sheath being covered with nano-filament of any of the NO-eluting polymers according to above, such as polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) and B-PEI
10 (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible, after the release of nitrogen oxide. Fig. 1A shows such a condom/sheath in a rolled-up form 10, and put onto an exemplary toe in a rolled-on form 11. Fig. 1B shows such a condom/sheath in a
15 rolled-up form 14, and put onto an exemplary finger in a rolled-on form 15. A condom has for instance the advantage that it during storage and transportation offers a protection against an undesired release of NO prior to intended use, as the rolled-up form 10,14 of the
20 condom/sheath safely encloses the NO-releasing material, even if a NO releasing factor, for instance humidity, eventually should enter a package in which the condom/sheath is packed prior to use.

In another embodiment the condom/sheath is covered on
25 the inside with nano-filament of L-PEI.

This condom/sheath may be in any suitable size, such as a suitable size for rolling said condom/sheath over the thigh, arm, neck, head, foot etc., to be treated. These sizes may for example vary from small, medium, and large
30 sized condoms/sheaths in accordance with the different sizes, in respect of the different body parts, of persons in the population. The condom/sheath may even have a size suitable for covering a foot, such as a sock 24, or a foot-
condom/sheath, as shown in Fig. 2C, or other specific part
35 of the body, to be able to obtain a cosmetic treatment.

According to an embodiment, the condoms/sheaths are coated with NO eluting nano fibres. According to another embodiment the condoms/sheaths are made of, or comprise nanofilaments, e.g. made by electro or gas jet spinning.

5 According to a further embodiment the condoms/sheaths comprises microspheres eluting NO in use. Preferably the three aforementioned embodiments employ L-PEI material loaded with NO. Activation on NO release may be done by e.g. foot sweat, water sprayed onto the condoms/sheaths
10 immediately prior to use, or a water bag configured for releasing water upon activation, e.g. by pushing onto the bag thus bursting (see below).

When the NO-eluting condom/sheath according to certain embodiments is treated with or gets in contact with
15 the moisture, in form of secreted sweat, the NO-eluting condom/sheath starts to release NO to the area to be treated. Alternatively the device is moistured or wettened, with a proton donor, immediately prior to application or use for controlling or activating the NO release.

20 In another embodiment the condom/sheath is covered on the inside with NO-eluting nano-particles, or micro-spheres, according to above.

When the nano-particles, or micro-spheres, according to this embodiment, gets in contact with the secreted
25 moisture, in form of sweat, on the inside of the condom/sheath, they start to elute NO on the area to be treated.

In yet another embodiment the condom/sheath contains a small proton donor bag or sealed proton donor sponge.
30 This proton donor bag or sealed proton donor sponge is used to activate the elution of NO from the NO-eluting nano-particles, or micro-spheres. This proton donor bag or sealed proton donor sponge may be located in the tip of the condom/sheath according to the invention. Persons that not
35 easily sweat may be helped by the use of this embodiment.

In another embodiment of the present invention a nitric oxide eluting polymer is provided, and/or combined, with microencapsulated proton donor.

This may for example be done by first manufacture
5 micro capsules, containing a proton donor, such as water or water containing liquid, in a state of the art manner. These micro capsules are then applied on the NO eluting polymer. The application of the micro capsules on the NO eluting polymer may for example be done by gluing, such as
10 pattern gluing, or instead spinning the NO eluting polymer onto said micro capsules. In this way a device or a system, comprising NO eluting polymer and micro encapsulated proton donor is manufactured. When the device or system is applied on the target area the device or system is compressed or
15 squeezed. Said compression or squeezing results in breakage of the micro capsules. The NO eluting polymer is thus exposed to proton donor, and the elution of NO from the NO eluting polymer is initiated on the target area. In other embodiments of the present invention the proton donor
20 inside the micro capsules is released by heating or shearing the micro capsules until the micro capsules are ruptured.

In still another embodiment the micro capsules are formed into a film, tape, or sheath. Thereafter, a film,
25 tape, or sheath of an NO eluting polymer is glued onto the film, tape, or sheath of micro capsules. Preferably the film, tape, or sheath of the NO eluting polymer is glued onto the film, tape, or sheath of the micro capsules in patterned way. The obtained pattern includes spaces where
30 there is no glue, in which spaces the proton donor will be transported to the NO eluting polymer once the micro capsules are broken from compression or squeezing. When the proton donor gets in contact with the NO eluting polymer the elution of NO starts. Thus, the combination of film,
35 tape, or sheath of micro capsules and NO eluting polymer

may be applied on a target area. Thereafter the combination is compressed or squeezed, which results in that the target area is exposed to NO.

In yet another embodiment the NO eluting polymer is spun directly onto the film, tape, or sheath of micro capsules, containing proton donor. The combination of film, tape, or sheath of micro capsules and spun NO eluting polymer may be applied on a target area. Thereafter the combination is compressed or squeezed, which results in that the target area is exposed to NO.

In still another embodiment of the present invention the device or system is provided with an activation indicator. This activation indicator indicates when the micro capsules are satisfyingly broken, hence when the NO eluting polymer is subjected to enough proton donor to elute an efficient amount of NO. This activation indicator may for example be obtained by colouring the proton donor that is trapped inside the micro capsules. When the micro capsules are broken the coloured proton donor escapes the microcapsules and the colour gets visualised while efficiently wetting the NO eluting polymer. Another way of obtaining an activation indicator is to choose to manufacture the micro capsules in a material, or choose a wall thickness of said micro particles, that creates a sound when the micro capsules break. It is also possible to admix a scent in the proton donor, contained in the micro capsules. This results in that the user of the device or system may smell the scent when the proton donor escapes from the micro capsules after breakage thereof.

In another embodiment a substance that changes color when it comes in contact with water may be incorporated in embodiments of the inventive device. Thus when the water capsules or water bag breaks the material changes color, thereby indicating that the material is activated. This may also comprise the subsequent activation of different areas

of a cosmetic treatment device in order to prolong the usable period of such a device.

In another embodiment of the present invention the device or system only allows directed target NO-elution in one direction. In this kind of embodiment one side of the device according to the invention has low permeability, or substantially no permeability, to nitric oxide. This may be accomplished by applying a material on one side of the device according to the invention that is not permeable to NO. Such materials may be chosen from the group comprising common plastics, such as fluoropolymers, polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. This embodiment is also easy to manufacture as the NO eluting polymer, e.g. L-PEI (or nitric oxide eluting polymer and carrier material, which will be explained in more detail below) may be electro or gas-jet spun onto the surface of the device according to the invention of e.g. the mentioned plastics, latex, or cotton.

In still another embodiment the device is provided with one membrane, which is permeable to nitric oxide, on a first side of the device, and another membrane, which has low permeability or substantially no permeability to nitric oxide, on a second side of said device. This embodiment provides the possibility to direct the elution to said first side of the device, while the elution of nitric oxide is substantially prevented from said second side. Thereby, a greater amount of nitric oxide will reach the intended area to be treated, rendering the device more effective.

The activation of the nitric oxide eluting polymer may be accomplished by contacting said polymer with a suitable proton donor. In one embodiment the proton donor may be selected from the group comprising water, body
5 fluids (blood, lymph, bile, etc.), alcohols (methanol, ethanol, propanols, buthanols, pentanols, hexanols, phenols, naphtols, polyols, etc.), aqueous acidic buffers (phosphates, succinates, carbonates, acetates, formats, propionates, butyrates, fatty acids, amino acids, etc.), or
10 any combinations of these.

By adding a surfactant in the proton donor one can facilitate the wettening of the device. The surfactant lowers the surface tension and the activating fluid is easily transported throughout the device.

15 In still another embodiment of the device, said device may be manufactured in the form of a polyurethane, or polyethylene, tape 22 or coating 20, according to Figs. 2A or 2B. This polyurethane tape or coating may easily be wrapped around, or applied on, the area to be cosmetically
20 treated. At least the side facing the body part, may be covered with NO-eluting nano-particles, or micro-spheres, or nano-filament of NO-eluting L-PEI. When these particles or filaments get in contact with the moisture, in form of sweat, on the inside of the tape or coating, the elution of
25 NO starts. When the tape/coating on the exterior is has a gas tight layer, directed target treatment with released NO is implementable.

For certain embodiments, a gas permeable layer may be provided for towards the cosmetic treatment area. This gas
30 permeable layer may further be liquid impermeable, such as made of Gore-Tex® or a similar material. In this manner the target area is kept dry from an eventually used NO releasing activation liquid, offering more comfort to the user of the cosmetic device.

In another embodiment of the device according to the present invention, said device is in form of a patch/pad 30, according to Fig. 3, which patch/pad is suitable to be applied on the face, arm, hand, thigh, back, stomach, neck, to be cosmetically treated, or onto other areas that are difficult to cover with the condom/sheath according to the present invention. This patch/pad 30 is attached by any suitable adhering means, such as materials that adhere to the skin.

Of course, in other embodiments of the invention, the patch/pad or tape/coating may be manufactured by any other suitable material, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. The NO-eluting polymer may be integrated in, spun together with, or spun on top of, any of these materials in all of the embodiments of the present invention.

In another embodiment these nano-particles, or microspheres, may be integrated in a soluble film that disintegrates on the inside of the condom/sheath or tape/coating according to the present invention, in order to elute NO at the area of interest when the soluble film gets in contact with the moisture, in form of sweat or from the water bag or sealed water sponge, on the area to be treated.

When placed on an area to be treated the device according to the present invention provides prevention and treatment of cosmetic disorders, caused by of chronological age, environmental factors, changes in physiological functions of skin, psoriasis, dermatitis, cellulites, viral

and/or bacteriological attacks, for example herpes, such as Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Epstein Barr Virus (EBV), CytoMegaloVirus (CMV), Varicella Zoster Virus (VZV), human herpes virus 6
5 (*exanthum subitum* and *roseola infantum*), human herpes virus 8 (HHV-8), caposis sarcoma, probably caused by HHV-8, warts, such as *verruca vulgaris*, *verruca planae*, *verruca seborroica*, filiform warts, mosaic warts, etc., caused by virus, and molluscs, caused by poxvirus.

10 In another embodiment of the present invention the device only allows NO-elution in one direction. In this kind of embodiment one side of the condom/sheath or tape/coating is non-permeable to NO. This may be accomplished by applying a material on one side of the
15 condom/sheath or tape/coating that is not permeable to NO. Such materials may be chosen from the group comprising common plastics, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates,
20 polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.
25 This embodiment is also easy to manufacture as the NO eluting polymer, e.g. L-PEI nano fibres may be electro or gas-jet spun onto the surface of a condom sheath of e.g. the mentioned plastics, latex, or cotton. In the case of a condom it may be rolled up, or a sheath may be turned
30 outside in after manufacturing to protect the NO eluting polymer during packaging, transport and prior to use from external influences, being e.g. mechanical (abrasion of the polymer), chemical (moisture deactivating the device prior to use) etc.

In yet another embodiment the NO-eluting device is acting as a booster for drug eluting patches, i.e. the device comprises additional agents e.g. pharmaceuticals, vitamins, nicotin, nitroglycerin, diclofenac etc. This
5 embodiment presents a device with the advantage of combining two treatments, of significant value, in one treatment.

Hence, a synergetic effect may be achieved by such devices when NO that is eluted from the device. NO has a
10 vasodilatory effect on the region where the device having the combination compound actuates. Vasodilated tissue is more susceptible to certain medications and thus more easily treated by the medical preparations and still NO has in addition to that the anti-inflammatory, anti-bacterial
15 etc. effect. Hence, an unexpected surprisingly effective treatment is provided.

The cosmetic treatment with NO eluted from a polymer may also be combined with other agents in order to enhance the cosmetic treatment, for instance a desquamating agent,
20 a moisturizer, a depigmenting or propigmenting agent, an anti-glycation agent, a 5.alpha.-reductase inhibitor, a lysyl and/or prolyl hydroxylase inhibitor, an agent for stimulating the synthesis of dermal or epidermal macromolecules and/or for preventing their degradation, an
25 agent for stimulating keratinocyte proliferation and/or differentiation, a muscle relaxant, a further antimicrobial agent, a tensioning agent, an anti-pollution agent or a free-radical scavenger, or a combination thereof.

Preferably the NO eluting polymer is prepared and
30 provided in a suitable form for topical application to keratin materials, including e.g. the skin, the eyelashes and the nails. The cosmetic use of a NO eluting polymer composition is for instance used for improving the appearance of such keratin materials. The cosmetic therapy
35 includes a variety of fields, such as a use for preventing

or treating wrinkles and fine lines and/or the loss of firmness, tonicity and/or elasticity of the skin and/or a dull complexion and/or dilation of the pores and/or skin or hair pigmentation disorders and/or skin dryness and/or

5 hyperseborrhea and/or sensitive skin, and/or eventually hair loss and/or baldness. The composition or preparation comprising the NO eluting polymer should be provided in a biocompatible and/or a physiologically acceptable medium, suitable for the topical application to the keratine

10 material mentioned above. Suitable forms include also moisturizing creams, anti-ageing creams, skin-peeling preparations. An alternative field of application is for cosmetically fading out pigmentary marks, in particular age marks. Moreover, cosmetic skin defects caused by acne may

15 be cosmetically treated by topical treatment with a device according to certain embodiments of the invention. Microbial colonization and inflammation may be removed in order to improve the appearance of acne exposed skin, for instance by the anti-inflammatory potency and/or the

20 antibacterial potency without inducing bacterial resistance of NO.

One of the most common infections in the world is caused by Human Papilloma Virus (HPV), commonly known as the warts virus. It is a microscopic virus particle that

25 infects the skin, causing warts or genital warts. The warts / genital warts appear as single bumps or in clusters some having a cauliflower structure. There are many strains or types of the HPV (warts) virus. The warts virus is also found in the genital area in men and woman (Genital Warts)

30 including in and around the anus, vagina, and penis, otherwise known as anal warts, vaginal warts and penis warts.

Genital Warts and HPV are a serious health concern. For woman, genital warts (vaginal) have been linked to

35 cervical as well as other types of genital cancers. Male

genital warts and female genital warts can also lead to cancer. Male genital warts are extremely common, and genital warts are as common in woman too. It is therefore extremely important to treat genital warts as soon as you
5 are aware of their presence. Any sexual or skin to skin contact with other people should be avoided the genital warts are removed, otherwise there is a substantial risk of passing the HPV virus on, and possibly infecting others with genital warts too. The device herein described may
10 therapeutically treat such warts advantageously. However, the present application is directed to the cosmetic side effects of such warts, e.g. scars formed during or after the removal of the warts. The device of some embodiments of the invention may be applied topically onto the genital
15 warts or regular warts using e.g. a cotton stick.

Certain embodiments may provide for cosmetic scar reduction.

Erectile dysfunction, or ED, can be a total inability to achieve erection, an inconsistent ability to do so, or a
20 tendency to sustain only brief erections. These variations make defining ED and estimating its incidence difficult. Estimates range from 15 million to 30 million, depending on the definition used. According to the National Ambulatory Medical Care Survey (NAMCS), for every 1,000 men in the
25 United States, 7.7 physician office visits were made for ED in 1985. By 1999, that rate had nearly tripled to 22.3. The increase happened gradually, presumably as treatments such as vacuum devices and injectable drugs became more widely available and discussing erectile function became accepted.
30 Perhaps the most publicized advance was the introduction of the oral drug sildenafil citrate (Viagra) in March 1998. NAMCS data on new drugs show an estimated 2.6 million mentions of Viagra at physician office visits in 1999, and one-third of those mentions occurred during visits for a
35 diagnosis other than ED.

In older men, ED usually has a physical cause, such as disease, injury, or side effects of drugs. Any disorder that causes injury to the nerves or impairs blood flow in the penis has the potential to cause ED. Incidence
5 increases with age: About 5 percent of 40-year-old men and between 15 and 25 percent of 65-year-old men experience ED.

The internal structure of the penis consists of two cylinder-shaped vascular tissue bodies (corpora cavernosa) that run throughout the penis; the urethra (tube for
10 expelling urine and ejaculate); erectile tissue surrounding the urethra; two main arteries; and several veins and nerves. The longest part of the penis is the shaft, at the end of which is the head, or glans penis. The opening at the tip of the glans, which allows for urination and
15 ejaculation, is the meatus. The physiological process of erection begins in the brain and involves the nervous and vascular systems. Neurotransmitters in the brain (e.g., epinephrine, acetylcholine, nitric oxide) are some of the chemicals that initiate it. Physical or psychological
20 stimulation (arousal) causes nerves to send messages to the vascular system, which results in significant blood flow to the penis. Two arteries in the penis supply blood to erectile tissue and the corpora cavernosa, which become engorged and expand as a result of increased blood flow and
25 pressure. Because blood must stay in the penis to maintain rigidity, erectile tissue is enclosed by fibrous elastic sheathes (tunicae) that cinch to prevent blood from leaving the penis during erection. When stimulation ends, or following ejaculation, pressure in the penis decreases,
30 blood is released, and the penis resumes its normal shape.

A usual method of treatment for ED is that oral medications are used to treat erectile dysfunction include selective enzyme inhibitors, e.g., sildenafil (ViagraTM), vardenafil HCl (LevitraTM), tadalafil (CialisTM) and
35 yohimbine (YohimbineTM). Selective enzyme inhibitors are

may be taken up to once a day to treat ED. They improve partial erections by inhibiting the enzyme that facilitates their reduction and increase levels of cyclic guanosine monophosphate (cGMP, a chemical factor in metabolism),
5 which causes the smooth muscles of the penis to relax, enabling blood to flow into the corpora cavernosa. However, patients taking nitrate drugs (used to treat chest pain) and those taking alpha-blockers (used to treat high blood pressure and benign prostatic hyperplasia) should not take
10 selective enzyme inhibitors. Men who have had a heart attack or stroke within the past 6 months and those with certain medical conditions (e.g., uncontrolled high blood pressure, severe low blood pressure or liver disease, unstable angina) that make sexual activity inadvisable
15 should not take Cialis™. Dosages of the drug should be limited in patients with kidney or liver disorders. Viagra™ is absorbed and processed rapidly by the body and is usually taken 30 minutes to 1 hour before intercourse. Results vary depending on the cause of erectile
20 dysfunction, and studies have shown that Viagra is not always effective, e.g. it helps men with erectile dysfunction associated with diabetes mellitus in 57% and radical prostatectomy in 43%. within 30 minutes and enhances the ability to achieve erection for up to 36
25 hours. Common side effects of selective enzyme inhibitors include headache, reddening of the face and neck (flushing), indigestion, and nasal congestion. Cialis™ may cause muscle aches and back pain. Yohimbine improves erections for a small percentage of men. It stimulates the
30 parasympathetic nervous system, which is linked to erection, and may increase libido. It is necessary to take the medication for 6 to 8 weeks before determining whether it will work or not. Yohimbine has a stimulatory effect and side effects include elevated heart rate and blood
35 pressure, mild dizziness, nervousness, and irritability.

Yohimbine's effects have not been studied thoroughly, but some studies suggest that 10% to 20% of men respond to treatment with the drug.

Self-injection involves using a short needle to
5 inject medication through the side of the penis directly into the corpus cavernosum, which produces an erection that lasts from 30 minutes to several hours. Side effects of such self-injections include infection, bleeding, and bruising at the injection site, dizziness, heart
10 palpitations, and flushing. There is a small risk for priapism, i.e. an erection that lasts for more than 6 hours and requires medical relief. Repeated injection may cause scarring of erectile tissue, which can further impair erection.

15 The device herein described may therapeutically treat erectile dysfunction, without the above-mentioned side-effects. For instance the herein described condom is well suited for this purpose, as well as other embodiments, e.g. gels or creams. However, the present application is
20 directed to the treatment of possible cosmetic side effects of conventional ED treatments, e.g. the above-mentioned scars resulting from self-injections.

The cosmetic treatment device elutes according to certain embodiments nitric oxide (NO) from an eluting
25 polymer in a therapeutic dose, such as between 0.001 to 5000 ppm, such as 0.01 to 3000 ppm, such as 0.1 to 1000 ppm, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 30 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 ppm. The concentration may vary widely depending on where the
35 concentration is measured. If the concentration is measured

close to the actual NO eluting polymer the concentration may be as high as thousands of ppm, while the concentration inside the tissue in this case often is considerably lower, such as between 1 to 1000 ppm.

5 Three important factors in controlling and regulating the elution of nitric oxide from a nitric oxide eluting polymer are how quickly a proton donor comes in contact with the nitric oxide releasing polymer, such as a diazolumdiolate group, the acidity of the environment
10 surrounding the nitric oxide eluting polymer, and the temperature of the environment surrounding the nitric oxide releasing polymer (higher temperature promotes elution of nitric oxide).

 In the embodiments of the present invention it may be
15 suitable to control or regulate the time span of NO release from the device according to the invention. This may be accomplished by integrating other polymers or materials in said device. These polymers or materials may be chosen from any suitable material or polymer, such as polyethylene,
20 polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl
25 Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

 In one embodiment of the present invention a nitric
oxide eluting polymer, such as L-PEI-NO, is mixed with a
30 carrier polymer to slow down or prolong the elution of nitric oxide. Also, in another embodiment, the nitric oxide eluting polymer may be mixed with more than one carrier polymer, whereby the elution or release may be tailor made to fit specific needs. Such a need may for example be a low
35 elution during a first period of time, when the environment

of the nitric oxide eluting polymer is hydrophobic, and a faster elution during a second period of time, when the environment of the nitric oxide eluting polymer has been altered to be more hydrophilic. This may for example be accomplished by using biodegradable polymers, whereby a low elution during a first period of time is obtained, after which, when the hydrophobic polymer has been dissolved, the hydrophilic polymer provides a higher elution of nitric oxide. Thus, a more hydrophobic carrier polymer will give a slower elution of nitric oxide, since the activating proton donor, such as water or body fluid, will penetrate the carrier polymer slower. On the other hand, a hydrophilic polymer acts the opposite way. One example of an hydrophilic polymer is polyethylene oxide, and one example of an hydrophobic polymer is polystyrene. These carrier polymers may be mixed with the nitric oxide eluting polymer and then electrospun to suitable fibers. The skilled person in the art knows which other polymers may be used for similar purposes. Fig. 4 illustrates two elution profiles (NO concentration vs. time) for two different polymer mixtures; a nitric oxide eluting polymer mixed with a hydrophilic carrier polymer in an acidic environment (A), and a nitric oxide eluting polymer mixed with a hydrophobic carrier polymer in a neutral environment (B).

In one embodiment this carrier polymer is substituted by another material with hydrophobic or hydrophilic properties. Therefore, the term "carrier material" in the present context should be interpreted to include carrier polymers and other materials with hydrophilic or hydrophobic properties. Some embodiments may also comprise using different hydrogels in order to suitably incorporate different release characteristics.

In another embodiment of the present invention the elution of nitric oxide from a nitric oxide eluting polymer, such as L-PEI-NO, is influenced by the presence of

protons. This means that a more acidic environment provides a quicker elution of nitric oxide. By activating the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, with an acidic fluid, such as
5 an ascorbic acid solution, the elution of nitric oxide may be accelerated.

The carrier polymers and carrier materials mentioned above may in addition affect other characteristics than the regulation of nitric oxide elution. An example of such a
10 characteristic is mechanical strength. Hence, advantageous devices may be produced according to specific application requirements.

In respect of the carrier polymers or carrier materials, the NO-eluting polymer may be integrated in,
15 spun together with, or spun on top of, any of these materials in all of the embodiments of the present invention. This spinning includes electro spinning, air spinning, dry spinning, wet spinning, melt spinning, and gel spinning. In this way, one may manufacture fibers of a
20 polymer mixture, comprising a nitric oxide eluting polymer and a carrier polymer, or a carrier material, with predefined nitric oxide eluting characteristics. These characteristics may be tailor made for different elution profiles in different applications.

25 The NO-eluting polymers in the devices according to the present invention may be combined with silver, such as hydroactivated silver. The integration of silver in the devices according to the present invention gives the healing process an extra boost. Preferably the silver is
30 releasable from the devices in the form of silver ions. The integration of silver in the device may present several advantages. One example of such an advantage is that the silver may keep the device in itself free from bacteria or viruses, while the nitric oxide eluting polymer elutes the
35 therapeutic dosage of nitric oxide to the target site.

The nitric oxide eluting polymer may comprise a secondary amine, either in the backbone or as a pendant, as described previously. This will make a good nitric oxide eluting polymer. The secondary amine should have a strong
5 negative charge to be easy to load with nitric oxide. If there is a ligand close to the secondary amine, such as on a neighbour atom, such as a carbon atom, to the nitrogen atom, with higher electronegativity than nitrogen (N), it is very difficult to load the polymer with nitric oxide. On
10 the other hand, if there is a electropositive ligand close to the secondary amine, such as on a neighbour atom, such as a carbon atom, to the nitrogen atom, the electronegativity of the amine will increase and thereby increase the possibility to load the nitric oxide elution
15 polymer with nitric oxide.

In an embodiment of the present invention the nitric oxide polymer may be stabilized with a salt. Since the nitric oxide eluting group, such as a diazeniumdiolate group, usually is negative, a positive counter ion, such as
20 a cation, may be used to stabilize the nitric oxide eluting group. This cation may for example be selected from the group comprising any cation from group 1 or group 2 in the periodic table, such as Na^+ , K^+ , Li^+ , Be^{2+} , Ca^{2+} , Mg^{2+} , Ba^{2+} , and/or Sr^{2+} . Different salts of the same nitric oxide
25 eluting polymer have different properties. In this way a suitable salt (or cation) may be selected for different purposes. Examples of cationic stabilized polymers are L-PEI-NO-Na, i.e. L-PEI diazeniumdiolate stabilized with sodium, and L-PEI-NO-Ca, i.e. L-PEI diazeniumdiolate
30 stabilized with calcium.

Another embodiment of the present invention comprises mixing the nitric oxide eluting polymer, or a mixture of the nitric oxide eluting polymer and a carrier material, with an absorbent agent. This embodiment provides the
35 advantage of an accelerated elution of nitric oxide since

the polymer, or polymer mixture, via the absorbent agent, may take up the activating fluid, such as water or body fluid, much faster. In one example 80 % (w/w) absorbent agent is mixed with the nitric oxide eluting polymer, or
5 mixture of nitric oxide eluting polymer and carrier material, and in another embodiment 10 to 50 % (w/w) absorbent agent is mixed with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material.

10 Since the elution of nitric oxide is activated by a proton donor, such as water, it may be an advantage to keep the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, in contact with said proton donor. If an indication requires an elution of
15 nitric oxide during a prolonged period of time, a system is advantageous, which presents the possibility to keep the proton donor in contact with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material. Therefore, in still another embodiment of
20 the present invention, the elution of nitric oxide may be regulated by adding an absorbent agent. The absorbent agent absorbs the proton donor, such as water, and keeps the proton donor in close contact with the nitric oxide eluting polymer during prolonged periods of time. Said absorbent
25 agent may be selected from the group comprising polyacrylates, polyethylene oxide, carboxymethylcellulose, and microcrystalline cellulose, cotton, and starch. This absorbent agent may also be used as a filling agent. In this case said filling agent may give the nitric oxide
30 eluting polymer, or mixture of said nitric oxide eluting polymer and a carrier material, a desired texture.

The device according to the present invention may be manufactured by, for example electro spinning of L-PEI or other polymers comprising L-PEI or being arranged in
35 combination with L-PEI. L-PEI is the charged at a

characteristic voltage, and a fine jet of L-PEI releases as a bundle of L-PEI polymer fibres. This jet of polymer fibres may be directed to a surface to be treated. The surface to be treated may for example be any suitable material in respect of a device according to the present invention. The electro spun fibres of L-PEI then attach on said material and form a coating/layer of L-PEI on the device according to the invention.

It is of course possible to electro spin the other NO-eluting polymers, according to above, on the device according to the invention while still being inside the scope of the present invention.

In one embodiment the NO-eluting polymers according to the present invention are electro spun in such way that pure NO-eluting polymer fibres may be obtained.

It is also within the scope of the present invention to electro spin a NO-eluting polymer together with other suitable polymer/polymers.

Gas stream spinning, air spinning, wet spinning, dry spinning, melt spinning, or gel spinning, of said NO-eluting polymers, or combination of nitric oxide eluting polymer and carrier material, is also within the scope of the present invention and has the advantage that application of the spun particles is not dependent on an electric charge to be applied. Hence, gas jet or air spinning is advantageous in certain fields of application, e.g. when inflammable solvents are present.

The manufacturing process according to the present invention presents the advantages of large contact surface of the NO-eluting polymer fibres with the area to be treated, effective use of NO-eluting polymer, and a cost effective way of producing the device according to the present invention.

The invention may be implemented in any suitable form. The elements and components of the embodiments

according to the invention may be physically, functionally,
and logically implemented in any suitable way or desired
arbitrary combination. Indeed, the functionality may be
implemented in a single unit, in a plurality of units, or
5 as part of other functional units.

Although the present invention has been described
above with reference to specific embodiments, it is not
intended to be limited to the specific form set forth
herein. Rather, the invention is limited only by the
10 accompanying claims and, other embodiments than the
specific above are equally possible within the scope of
these appended claims.

In the claims, the term "comprises/comprising" does
not exclude the presence of other elements or steps.
15 Furthermore, although individually listed, a plurality of
means, elements or method steps may be implemented.
Additionally, although individual features may be included
in different claims, these may possibly advantageously be
combined, and the inclusion in different claims does not
20 imply that a combination of features is not feasible and/or
advantageous. In addition, singular references do not
exclude a plurality. The terms "a", "an", "first", "second"
etc do not preclude a plurality. Reference signs in the
claims are provided merely as a clarifying example and
25 shall not be construed as limiting the scope of the claims
in any way.

CLAIMS

1. A device configured to cosmetically treat and/or prevent cosmetic disorders, including wrinkles, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks, at a cosmetic treatment site of a body, wherein said device comprises a nitric oxide (NO) eluting polymer configured to elute a cosmetic dosage of nitric oxide (NO) when used for said treatment and/or prevention, and wherein said device is configured to expose said cosmetic target site in or on a body to said nitric oxide (NO) when said polymer in use elutes nitric oxide (NO),
c h a r a c t e r i z e d i n t h a t
said nitric oxide (NO) eluting polymer is integrated with a carrier material, such that said carrier material, in use, regulates and controls the elution of said cosmetic dosage of nitric oxide (NO).
2. Device according to claim 1, wherein said nitric oxide (NO) eluting polymer comprises diazeniumdiolate groups, S-nitrosylated groups, and O-nitrosylated groups, or any combination these.
3. Device according to claim 1 or 2, wherein said nitric oxide (NO) eluting polymer is L-PEI (linear polyethyleneimine), loaded with nitric oxide (NO) through said diazeniumdiolate groups, S-nitrosylated groups, or O-nitrosylated groups, or any combination these, arranged to elute nitric oxide at said cosmetic treatment site of said cosmetic disorder at said body, for treatment of cosmetic disorders including wrinkles, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks, thereby.

4. Device according to claim 1, wherein said nitric oxide eluting polymer is selected from the group comprising amino cellulose, amino dextrans, chitosan, aminated chitosan, polyethyleneimine, PEI-cellulose, polypropyleneimine, polybutyleneimine, polyurethane, poly(buthanediol spermate), poly(iminocarbonate), polypeptide, Carboxy Methyl Cellulose (CMC), polystyrene, poly(vinyl chloride), and polydimethylsiloxane, or any combinations of these, and these mentioned polymers grafted to an inert backbone, such as a polysaccharide backbone or cellulosic backbone.

5. Device according to claim 1, wherein said device has a form selected from the group consisting of a condom/sheath (10,14), a sock (24), a patch/pad (30), and a tape/coating (20, 22), adapted to be applied on or at said cosmetic treatment site of said cosmetic disorder on said body for treatment of cosmetic disorders, including wrinkles, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks.

6. Device according to claim 5, wherein said condom/sheath (10, 14), sock (24), patch/pad (30), or tape/coating (20, 22) comprises polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these, including said nitric oxide (NO) eluting polymer configured for in use eluting said nitric oxide (NO) to said cosmetic treatment site of said cosmetic

disorder of a body for treatment of said cosmetic disorders, including wrinkles, acne, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks.

5

7. Device according to any of claims 1 to 6, including a proton donor carrier element, such as a proton donor bag, sealed proton donor sponge, or micro encapsulated water, configured for releasing a proton donor therefrom, when activated, to said device, and wherein said polymer is activatable to elute nitric oxide (NO) upon contact with said proton donor.

8. Device according to claim 7, wherein said proton donor is selected from the group comprising water, blood, lymph, bile, methanol, ethanol, propanols, butanols, pentanols, hexanols, phenols, naphtols, polyols, phosphates, succinates, carbonates, acetates, formats, propionates, butyrates, fatty acids, and amino acids, or any combinations of these.

9. Device according to claim 1, wherein said device is partly disintegrable when subjected to a proton donor.

10. Device according to claim 1 or 7, wherein said polymer comprises silver, configured for cosmetic treatment of said site of said cosmetic disorder on the body.

11. Device according to claim 1, wherein said nitric oxide eluting polymer is comprised in the device in form of fibers, nano-particles or micro-spheres.

12. Device according to claim 11, wherein said fibres, nano-particles, or micro-spheres, are integrated in a gel, cream, foam, or hydrogel, or combinations thereof.

13. Device according to claim 11, wherein said nano-particles, or micro-spheres, are integrated with, preferably encapsulated in, a material, selected from the group comprising polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

14. Device according to claim 11 or 12, wherein said device is a lipstick-like device or a dermatological ointment, cream or lotion.

15. Device according to claim 1, wherein said polymer is configured to act as a booster for drug eluting patches when used.

16. Device according to claim 1, wherein said carrier material is selected from the group consisting of polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.

17. Device according to claim 1, wherein said carrier material is a hydrogel.

18. Device according to claim 1, wherein the nitric oxide eluting polymer is activateable by proton donors, wherein a the nitric oxide eluting polymer is, prior to use, stored separate from the proton donor until initiation
5 of elution of nitric oxide therefrom.

19. Device according to claim 18, wherein the device is a syringe-type device having two separate containers, wherein a first container contains a proton donor-based NO
10 release activation agent, such as a gel, and a second container contains a non proton donor-based gel, comprising the nitric oxide eluting polymer, wherein the syringe-type device is configured to provide admixing upon administration to a cosmetic treatment site.

15

20. Device according to claim 1, wherein said nitric oxide eluting polymer comprises a secondary amine in the backbone or a secondary amine as a pendant.

20 21. Device according to claim 20, wherein a positive ligand is located on the neighbour atom to the secondary amine.

22. Device according to claim 1 or 16, comprising an
25 absorbent agent.

23. Device according to claim 22, wherein said absorbent agent is selected from the group comprising polyacrylate, polyethylene oxide, Carboxy Methyl Cellulose
30 (CMC), microcrystalline cellulose, cotton, or starch, or any combinations thereof.

24. Device according to claim 1, 16, 21 or 22, comprising a cation, said cation stabilizing the nitric
35 oxide eluting polymer.

25. Device according to claim 24, wherein said cation is selected from the group comprising Na^+ , K^+ , Li^+ , Be^{2+} , Ca^{2+} , Mg^{2+} , Ba^{2+} , and/or Sr^{2+} , or any combinations thereof.

5

26. A manufacturing process for a device configured to cosmetically treat or prevent cosmetic disorders, for instance caused by infections, including wrinkles, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks, according to claim 1, comprising:

selecting a nitric oxide (NO) eluting polymer configured to elute a cosmetic dosage of nitric oxide (NO) when used for said treatment and/or prevention,

15 selecting a carrier material, which carrier material is configured to regulate and control the elution of said cosmetic dosage of nitric oxide (NO),

incorporating the NO-eluting polymer with said carrier material into an nitric oxide (NO) eluting material, such that said carrier material, in use of said device, regulates and controls the elution of said cosmetic dosage of nitric oxide (NO), and

20 deploying said nitric oxide eluting material into a suitable form, or as a coating onto a carrier, to form at least a part of said device, such that said device is configured to expose a cosmetic target site in or on a body to said nitric oxide when said NO-eluting polymer in use elutes nitric oxide (NO).

30 27. The manufacturing process according to claim 26, wherein said deploying comprises electro spinning, air spinning, gas spinning, wet spinning, dry spinning, melt spinning, or gel spinning of NO-eluting polymer.

28. The manufacturing process according to claim 26 or 27, wherein said selecting said nitric oxide (NO) eluting polymer comprises selecting a plurality of nitric oxide (NO) eluting polymeric particles, preferably nano
5 fibres, nano particles or micro spheres.

29. The manufacturing process according to claim 26 or 27, wherein said incorporating said NO-eluting polymer with said carrier material comprises integrating said NO-
10 eluting polymer in said carrier material, spinning said NO-eluting polymer together with said carrier material, or spinning said NO-eluting polymer on top of said carrier material, in order to predefine nitric oxide eluting characteristics of said device.

15

30. The manufacturing process according to claim 26, further comprising integrating silver in said device.

31. The manufacturing process according to claim 26,
20 further comprising microencapsulating proton donor in micro capsules, and

applying the micro capsules to said nitric oxide (NO) eluting material.

25 32. The manufacturing process according to claim 31, wherein said applying comprises pattern gluing, or spinning the NO eluting material onto said micro capsules.

33. The manufacturing process according to claim 31,
30 comprising forming the micro capsules into a first film, tape, or sheath,

forming a second film, tape, or sheath of said NO eluting material, and

gluing the first film, tape, or sheath of micro capsules to said second film, tape, or sheath of said NO eluting material.

5 34. The manufacturing process according to claim 33, wherein said gluing comprises patterned gluing, such that a pattern is obtained including glue free spaces.

10 35. The manufacturing process according to claim 31, comprising forming the micro capsules into a first film, tape, or sheath, and directly spinning the NO eluting material onto the film, tape, or sheath of micro capsules, containing a proton donor.

15 36. The manufacturing process according to claim 31, comprising providing an activation indicator configured to indicate when the micro capsules are broken such that the NO eluting material is subjected to said proton donor to elute NO.

20

 37. The manufacturing process according to claim 36, wherein said providing an activation indicator comprises providing a coloring agent inside the micro capsules.

25 38. The manufacturing process according to claim 36, wherein said providing an activation indicator comprises selecting a material for the micro capsules, or choosing a wall thickness of said micro capsules, that creates a sound when the micro capsules break.

30

 39. The manufacturing process according to claim 36, wherein said providing an activation indicator comprises admixing a scent material into the micro capsules.

40. The manufacturing process according to claim 36, wherein said providing an activation indicator comprises providing a substance that changes color when it comes in contact with the proton donor.

5

41. Use of a nitric oxide (NO) eluting polymer for the manufacture of a device for the cosmetic treatment of cosmetic disorders, including wrinkles, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks,
wherein
nitric oxide is loaded to said device so said device elutes nitric oxide (NO) from said eluting polymer in a cosmetic dose when used at a site of cosmetic disorder on a body.

42. Use according to claim 41, wherein said cosmetic dose is 0.001 to 5000 ppm, such as 0.01 to 3000 ppm, such as 0.1 to 1000 ppm, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 ppm..

43. A method of cosmetically treating a cosmetic disorder, including wrinkles, cellulites, acne, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks, comprising
applying a device, that comprises a nitric oxide (NO) eluting polymer configured for eluting a cosmetic dosage of

nitrogen oxide (NO) when used for said cosmetic treatment and a carrier material, which carrier material regulates and controls the elution of said therapeutic dosage of nitric oxide (NO), and thereby

5 exposing said cosmetic treatment site of said cosmetic disorder on a body to said nitric oxide when said polymer in use elutes nitrogen oxide (NO) by eluting a cosmetic dose of nitric oxide from said nitric oxide eluting polymer to said treatment site.

10

44. The method according to claim 43, wherein said site of said cosmetic disorder is a selected body region including face, neck, shoulder, back, arm, hand, stomach, genital, thigh, leg, or foot, of a body, and wherein said
15 method comprises applying a condom/sheath, sock, patch/pad, and/or tape/coating or gel, cream, foam, or hydrogel, or combinations thereof, to said selected body region of said body, for said exposure.

20

45. The method according to claim 43 or 44, comprising

enhancing the cosmetic effect of a cosmetic treatment substance comprised in said device by said cosmetic dose of nitric oxide.

25

46. Use of nitric oxide (NO) to cosmetically treat and/or prevent cosmetic disorders, including wrinkles, cellulites, psoriasis, dermatitis, and viral and/or bacteriological attacks, such as herpes, caposis sarcoma, warts, and/or mollusks, at a cosmetic treatment site of a
30 body.

35

47. Use of nitric oxide (NO) to provide cosmetic scar reduction.

1/4

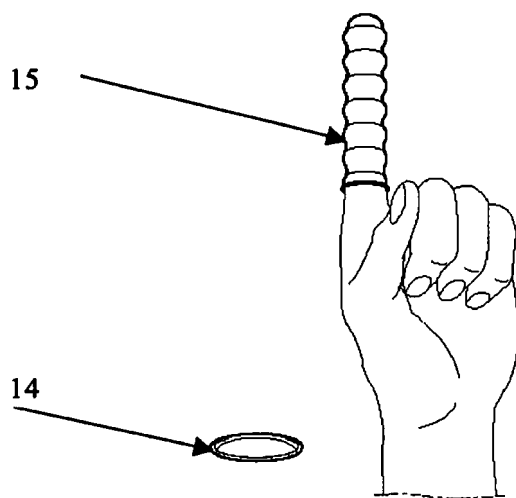
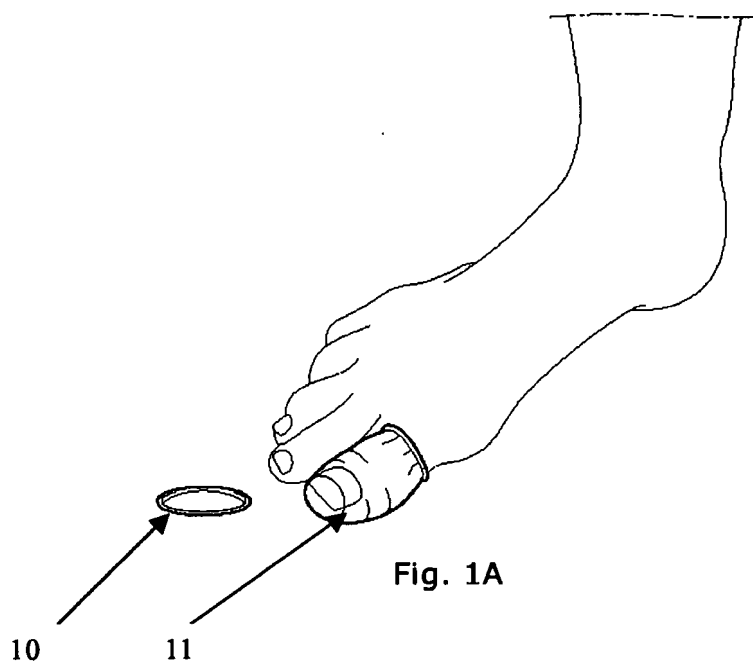


Fig. 1B

2/4

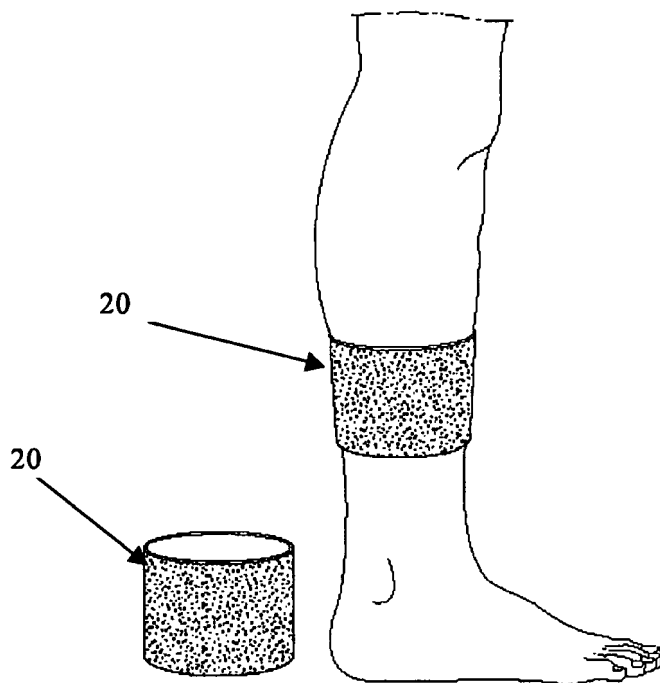


Fig. 2A

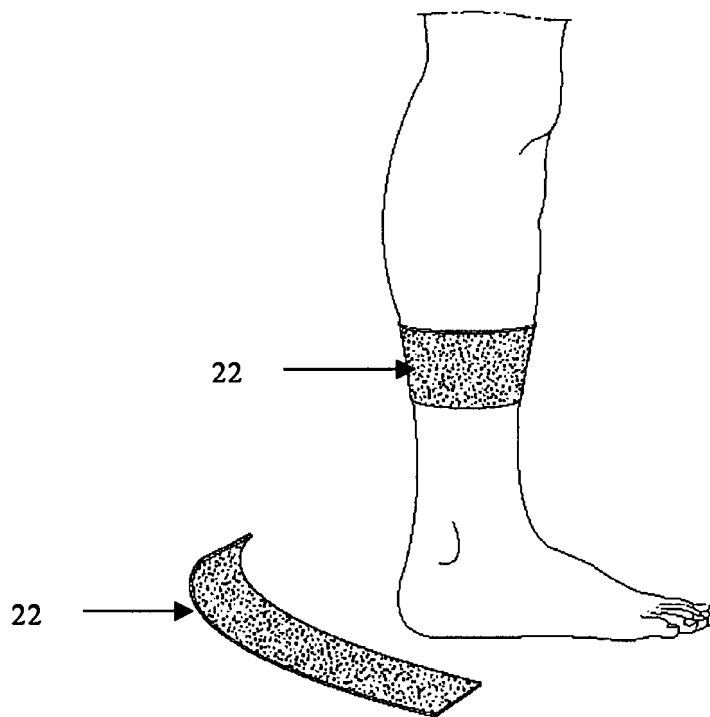
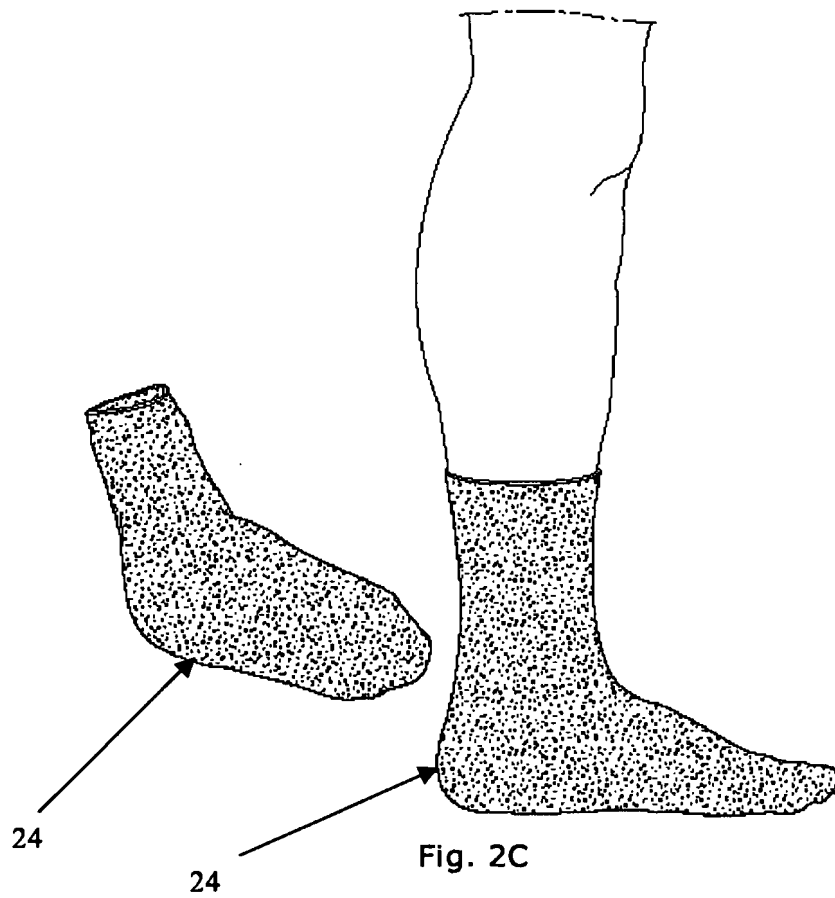


Fig. 2B

3/4



4/4

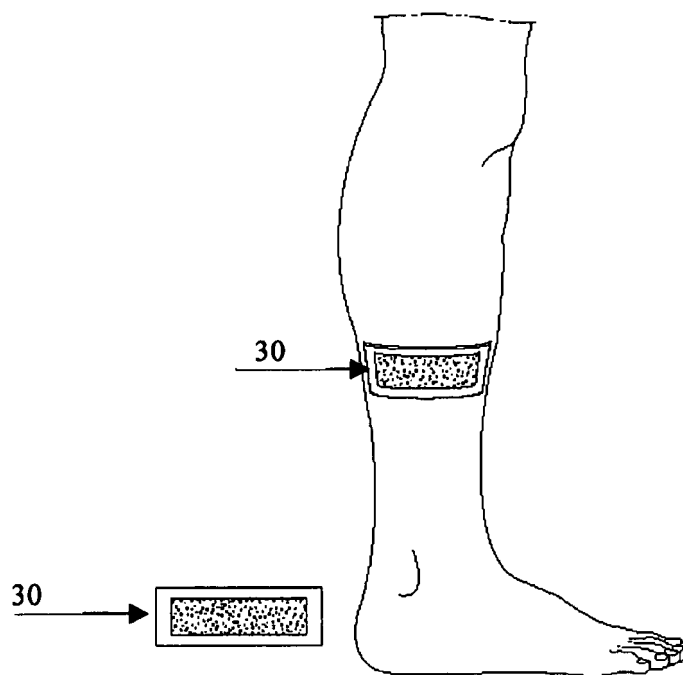


Fig. 3

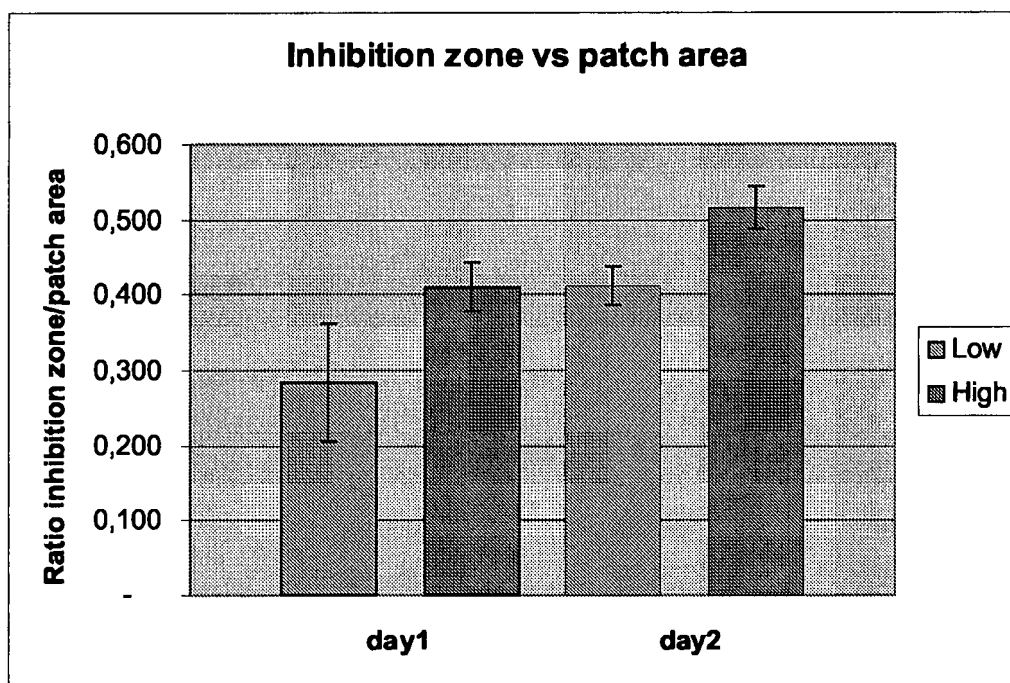


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/050884

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L15/44 A61L27/34 A61L27/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 2002/082221 A1 (HERRMANN ROBERT A ET AL) 27 June 2002 (2002-06-27)</p> <p>paragraph [0026] paragraph [0030] paragraph [0073] - paragraph [0074] paragraph [0078] paragraph [0125] paragraph [0128] claim 54</p> <p>----- -/-</p>	<p>1, 2, 5, 16, 26, 41, 43, 46</p>



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

28 June 2006

Date of mailing of the international search report

10/07/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Staber, B

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/050884

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SMITH D J ET AL: "Transdermal delivery of nitric oxide from diazeniumdiolates" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 51, no. 2-3, 12 February 1998 (1998-02-12), pages 153-159, XP004113622 ISSN: 0168-3659 abstract	1,2,4,5, 11,16, 26,41, 43,46
X	US 2002/094985 A1 (HERRMANN ROBERT A ET AL) 18 July 2002 (2002-07-18) paragraph [0026] paragraph [0037] paragraph [0058] - paragraph [0100] paragraph [0122] - paragraph [0125]	1-4,16, 26
X	US 5 405 919 A (KEEFER ET AL) 11 April 1995 (1995-04-11) column 3, line 21 - line 25 column 8, line 32 - line 44 column 8, line 60 - line 66	1-6,16
X	EP 1 300 424 A (MEDTRONIC AVE INC) 9 April 2003 (2003-04-09) paragraph [0018] paragraph [0032]	1-4,11, 16
A	US 2002/136750 A1 (BENJAMIN NIGEL ET AL) 26 September 2002 (2002-09-26) paragraph [0001] abstract	1-47

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/050884

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002082221 A1	27-06-2002	AU 2002246664 A1 CA 2443080 A1 EP 1343485 A2 JP 2004523520 T WO 02056874 A2 US 2004259840 A1	30-07-2002 25-07-2002 17-09-2003 05-08-2004 25-07-2002 23-12-2004
US 2002094985 A1	18-07-2002	CA 2443895 A1 EP 1399134 A2 JP 2005503834 T WO 02056864 A2 US 2004171589 A1	25-07-2002 24-03-2004 10-02-2005 25-07-2002 02-09-2004
US 5405919 A	11-04-1995	US 5525357 A US 5718892 A US 5676963 A US 5691423 A	11-06-1996 17-02-1998 14-10-1997 25-11-1997
EP 1300424 A	09-04-2003	JP 2003201313 A US 2005079148 A1 US 2003077243 A1	18-07-2003 14-04-2005 24-04-2003
US 2002136750 A1	26-09-2002	NONE	